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Initial Experience in a Community Hospital with Sentinel Lymph Node Mapping and Biopsy for Evaluation of Axillary Lymph Node Status in Palpable Invasive Breast Cancer

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Background and Objectives: To determine the sentinel node detection rate and the accuracy with which the sentinel node histology reflects that of the axilla in a series of patients with palpable invasive breast cancer.

Methods: Forty-four patients with clinically node-negative palpable invasive T1 or T2 breast tumors underwent sentinel node biopsy using isosulfan blue dye, followed immediately by either local excision of the primary lesion with standard axillary lymph node dissection or modified radical mastectomy. All surgeries were performed at Northwest Hospital, Seattle, Washington, between January 1996 and October 1997.

Results: The sentinel node was successfully identified in 73% of the patients (32/44). The frequency of sentinel node detection was greater for tumors in the outer quadrants than the inner quadrants (z-test, $P < 0.001$). Of the 32 patients in whom a sentinel node was identified, 10 (31%) had histologically positive sentinel nodes: 5 (16%) by frozen section, 2 additional patients (6%) after permanent hematoxalin-eosin (H&E) stained sections, and the remaining 3 (9%) after immunohistochemical stains for cytokeratins when the FS and permanent H&E-stained sections were benign. Twenty patients had benign axilla. The sentinel node was falsely negative in 2 patients, yielding an accuracy of 93.8%, sensitivity of 83.3%, and negative predictive value of 91%.

Conclusions: Lymphatic mapping is technically feasible for patients with small (T1 or T2) palpable invasive breast tumors. The sentinel node can be reliably identified in the majority of these patients, and its histology reflects that of the axilla with a high degree of accuracy. Immunohistochemical stains and permanent H&E-stained sections of the sentinel node increased the test's ability to correctly identify axillary metastases. Improving this sensitivity remains a primary goal, however, if benign sentinel node histology is to be used as a criterion to preclude axillary dissection.

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INTRODUCTION

Breast conservation is now considered an acceptable alternative to modified radical mastectomy for patients with small invasive tumors. However, the management of the axilla in the patient with breast cancer is currently a point of controversy. It is generally accepted that axillary lymph node dissection is not indicated for patients with ductal carcinoma in situ because of the low likelihood of axillary node involvement [1,2]. The controversy exists over the indication for axillary lymph node dissection in patients with small invasive tumors, with some authors recommending that patients with T1a lesions be spared a dissection [3]. In studies with pathologic follow-up on the axillae, the reported metastatic rate varies. Moezzi et al. [4] reported no axillary metastases in 28 patients with tumors $\leq$0.7 cm diameter. Silverstein et al. [5] reported the rate associated with T1a lesions at 3%, and that associated with T1b lesions at 17% (12% for T1a and T1b combined). Sinn et al. [6] reported these respective rates higher yet (10% for T1a and 19% for T1b). The combined T1a/T1b metastatic rate reported by Halverson et al. [7] was 12.4%, comparable to that reported by both Silverstein et al. and Sinn et al. [5,6]. These last three studies suggest that a significant number of patients with these types of lesions stand to benefit from accurate staging. For most solid tumors, the most powerful and predictive prognostic factor is the status of the regional lymph nodes [8]. For breast cancer, the presence of regional metastases decreases 5-year survival by about 28%–40% [9,10]. Unfortunately, complete axillary dissection often results in complications, such as arm lymphedema, that can significantly impact the patient's quality of life.

Sentinel node biopsy can potentially save a significant number of these patients axillary dissection and the complications that often accompany this surgery, while still providing information necessary for staging. Giuliano et al. [11] and others have previously described lymphatic mapping in breast cancer using isosulfan blue dye. Our objectives in this study were to evaluate our own ability to identify the sentinel node(s) using this method in a community hospital setting, and to determine the accuracy with which the sentinel node pathology reflects that of the axilla.

MATERIALS AND METHODS

This prospective study was conducted between January 1996 and October 1997. It was previously reviewed and approved by the Institutional Review Board at Northwest Hospital for the protection of human subjects. Patients included in the study were those to be staged with axillary lymph node dissection in the usual course of treatment for histologically documented invasive breast tumors that were both palpable and operable. Patients having undergone preoperative chemotherapy were eligible if they had a localizable tumor mass and breast surgery with axillary dissection was a planned part of their clinical management. Patients excluded from the study were those who were pregnant, had a known hypersensitivity to isosulfan blue dye or related compounds, had nonoperable breast cancer, had pure noninvasive breast cancer or benign disease, or had concurrent medical conditions for which general anesthesia and surgery on the breast were contraindicated. Patients with clinically positive axillae were also excluded. Eligible patients were educated concerning the details of the procedure, including risks and potential benefits, and were required to provide written consent if they chose to participate.

We used the lymphatic mapping and sentinel node lymphadenectomy techniques described by Giuliano et al. [11]. For the majority of patients (91%), the preoperative histological diagnosis was established by large-core needle biopsy. For these patients, isosulfan blue vital dye (Lymphazurin, Hirsch Industries, Richmond, VA) was injected closely around the breast mass using a 25-gauge needle. For 3 patients in whom the primary tumor had been excised previously, the dye was injected into the wall of the biopsy cavity and surrounding parenchyma. The dose was standardized at 4–6 ml. The interval between the dye injection and the axillary incision was standardized at about 5 min.

After the surgical area was draped, the initial incision was made at the lower edge of the hair-bearing area in the skin lines. Upon identifying a green-blue lymphatic channel, it was followed proximally to a blue-stained "sentinel" lymph node or nodes, the first to receive lymph from that particular area in the breast. This was not necessarily the lowest node. The sentinel node(s) were removed, then given to the pathologist who immediately performed frozen-section microscopic examination of representative sentinel node tissue. The pathologist informed the surgeon of the interpretation while the patient was still in the operating room. In this series, all patients underwent partial or complete mastectomy with axillary lymph node dissection.

Node tissue remaining after frozen section was fixed in 10% buffered formalin. The pathologist performed macroscopic examination of all tissue removed during surgery. The sentinel node was embedded in paraffin entirely in as many cassettes as necessary, as was a sample of all other nodes removed from the axilla. After

formalin fixation, the specimen submitted as "sentinel node" was palpated, then "bread-loafed" with a scalpel every 3–4 mm throughout. Each macroscopically identified lymph node was either bivalved longitudinally or cut into 3- to 4-mm-thick sections if it was >6 mm thick. All lymph node tissue was subsequently embedded in as many paraffin blocks as were necessary. Each block containing lymph node tissue was then faced with a microtome, and as many 4-μm-thick microsections that would fit were placed on one glass slide. Second and third glass slides were similarly prepared. One of the three slides from each block was stained with hematoxylin-eosin (H&E). Immunohistochemistry (IHC) preparations for antibodies to cytokeratin were made with the remaining two slides using the avidin-biotin technique, one as a positive and the other a negative control. All microscopic tissue examinations were performed using the transmitted bright field technique. We do not routinely prepare microsections at intervals into paraffin-embedded blocks. If suspicious cells are identified that are not diagnostic, additional microsections may be prepared for microscopic examination at the discretion of the responsible pathologist.

The details of macroscopic and microscopic features of each specimen were reported. The report included a pathologist's interpretation of the frozen section slides, the H&E-stained slides, and the IHC studies. All laboratory examinations were conducted in the Northwest Hospital Laboratory, which is accredited under the College of American Patholgoists Laboratory Accreditation Program.

Study data were compiled using predesigned data collection form, which was completed by the patient's surgeon. The form was then routed to the Northwest Hospital Clinical Research Coordinator, who was responsible for updating and maintaining an electronic database. Results were verified using copies of each patients laboratory report. Results and procedures were periodically reviewed to ensure conformance to the design protocol.

RESULTS

This series comprised 44 women who underwent intraoperative lymphatic mapping using the isosulfan blue dye technique at Northwest Hospital in Seattle between January 15, 1996 and October 24, 1997. Northwest Hospital is a medium-sized community general hospital located in the North Seattle suburbs.

Immediately following lymphatic mapping with or without sentinel node lymphadenectomy, all 44 patients underwent either local excision of the primary tumor and axillary node dissection (30 patients, 68%) or modified radical mastectomy (14 patients, 32%). Their mean age was 65 years (range, 36–83). Patient demographics are summarized in Table I. The diagnosis of carcinoma was established prior to this surgery for all 44 patients, 40 (91%) by large core needle biopsy, 3 (7%) by excisional biopsy, and 1 (2%) by fine-needle aspiration. The size, location, and histology of the primary tumors are summarized in Table II. The majority of tumors (66%) were T1 infiltrating ductal carcinomas located in one of the outer two quadrants.

TABLE I. Patient Demographics for 44 Women with Palpable Invasive Breast Cancer, Who Underwent Sentinel Lymph Node Mapping and Biopsy Followed by Either Partial Mastectomy With Axillary Dissection (ALND) or Modified Radical Mastectomy at a Single Institution

Characteristic	No. (%) of patients[a]
Total no. of patients	44
Mean age	65 years
Age range	36–83 years
No. premenopausal (%)	11 (25)
No. postmenopausal (%)	33 (75)
Mode of tumor diagnosis, no. (%)	
Large-core needle biopsy	40 (91)
Excisional biopsy	3 (7)
Fine-needle aspiration	1 (2)
Operative procedure, no. (%)	
Partial mastectomy and ALND	30 (68)
Modified radical mastectomy	14 (32)

[a]Unless specified otherwise.

Figure 1 shows our rate of success in identifying the sentinel node(s) and the resulting histology of sentinel nodes relative to the regional lymphatic basin, by number of cases. At least 1 sentinel node was successfully identified and excised for histologic evaluation in 32 cases (73%). The average number of sentinel nodes excised per case was 1.1 (range, 1–2). Two sentinel nodes were identified in 3 patients, for a total of 35 sentinel nodes. As Giuliano et al. reported [11], we also found a learning curve associated with the rate of sentinel node detection (Fig. 2). In addition, we found sentinel node detection more likely to be successful for patients with tumors in the outer quadrants compared to those with tumors in the inner quadrants (Fischer's exact test, $P < 0.001$). Tumor size, Bloom-Richardson scale, and degree of tumor differentiation were not statistically predictive of successful sentinel node detection.

Of 32 cases in which at least 1 sentinel node was identified, the sentinel node histology accurately reflected that of the axilla in 30 (93.8%). Twenty cases (62.5%) were true negatives (sentinel node and remainder of axilla negative). Ten cases (31.3%) were true positives (sentinel node(s) alone positive or sentinel node(s) plus additional positive node(s) in the remainder of the axilla). In 2 cases (6.3%), the sentinel node was falsely negative (sentinel node negative by all tests with at least 1 additional positive node in the remainder of the axilla). The ability of the sentinel node histology to correctly identify disease in the axilla (sensitivity) is, therefore, 83.3% (10/12), with a negative predictive value of 91%

TABLE II. Size, Location, and Histology of Primary Palpable Invasive Breast Tumor in 44 Patients

	No. of patients (%)[a]
Location	
Laterality	
Right	23 (52)
Left	21 (48)
Quadrant	
Upper outer	22 (50)
Lower outer	11 (25)
Upper inner	7 (16)
Lower inner	4 (9)
Histology	
Infiltrating ductal	37 (84)
Infiltrating lobular	6 (14)
Papillary	1 (2)
Combined Bloom-Richardson score	
Mean	6.34
Range	4–9
Size	
Mean	1.8 cm
Range	0.5–5 cm
T1	34 (77)
T2	10 (23)

[a]Unless specified otherwise.

(20/22). The specificity and the negative predictive value are both 100% because there are, by definition, no false positives (i.e., if the sentinel node is positive, the axilla is positive).

Of the 10-true-positive cases, the sentinel node was positive by frozen section in 5. In 2 cases, the sentinel node was negative by frozen section but contained micrometastases on permanent H&E-stained sections. In the remaining 3 cases, the sentinel node was negative by both frozen section and permanent H&E-stained sections but by IHC contained micrometastases. If the status of the sentinel node was to be used as criterion for axillary dissection, these 5 patients would not have undergone axillary dissection during the initial surgery and would have required a second surgery for that.

Of 35 total sentinel nodes found in 32 patients, 10 (28.6%) were eventually diagnosed positive for metastatic disease, by frozen section, permanent H&E-stained sections, or IHC. Of 400 total nonsentinel axillary nodes removed, 26 (6.5%) were positive for metastatic disease. The median number of nonsentinel nodes removed was 9 (range, 3–20).

DISCUSSION

The patient's potential to benefit from sentinel node mapping/biopsy is contingent on the surgeon's ability to successfully identify the sentinel node(s), the accuracy with which the sentinel node histology reflects that of the axilla, and the likelihood that their sentinel node(s) will be negative.

In this series, we could identify at least 1 sentinel node in 73% of the cases. This rate is comparable, if not slightly higher, than that reported by Giuliano et al. [11] using the blue dye technique alone. A number of studies now indicate that combining lymphoscintigraphy with the blue dye technique can improve the sentinel node detection rate [12,13]. Subsequent to this series, we have incorporated lymphoscintigraphy into our sentinel node mapping protocol and increased our sentinel node detection rate by >10%. Lymphoscintigraphy adds a degree of complication to the logistics of patient management. We recommend carefully flow-charting patient management through the entire process first to ensure good cooperation between the radiology and surgical staffs. We incorporated these techniques in stages at our institution, performing the controlled blue-node-only study described here for the first 44 patients and then adding lymphoscintigraphy. With careful planning, we believe these procedures can be incorporated simultaneously. However, in so doing, one loses the ability to determine the added benefit of the lymphoscintigraphy.

In the majority of our cases (93%), sentinel node mapping was performed prior to removal of the primary tumor. Of 3 cases in which the tumor was surgically removed beforehand, we failed to identify the sentinel node in 2. Mapping can be done by injecting the dye around the resulting cavity; however, damaged lymphatics and/or other factors may block the uptake of dye and decrease the chances of successful sentinel node detection. In general, we perform large-core needle biopsies for palpable and nonpalpable breast lesions with the goal of performing only one definitive operation. Large-core needle biopsy has been shown to be as accurate and less costly for breast cancer diagnosis than excisional biopsy [14,15].

As reported by Giuliano et al. [11], we also found a definite learning curve associated with the blue dye technique. Our sentinel node detection rate improved over the course of this series, and approached 80% in the latter third of these cases (Fig. 2). As a result of this study, we have established a program and guidelines whereby surgeons unfamiliar with the procedure can acquire instruction and become certified.

For cases in which a sentinel node was identified, we found its histology to reflect that of the axilla with an accuracy of 93.8%. This is lower than that reported by others, but in this series, we sampled an average of only 1.1 nodes per case (maximum 2) compared to an average of ≥ 2 in comparable series. We sampled only nodes that turned blue. It is uncertain whether or not, given more time, additional nodes will stain blue. In case no. 2 of our series, the patient's 1-cm tumor was located high in the upper-outer quadrant. The only positive node was immediately adjacent to the sentinel node, which was negative. It is possible that, given more time, this sentinel node wound also have stained blue. In fact, the rate at which dye is taken up in the lymphatic tracts will be different

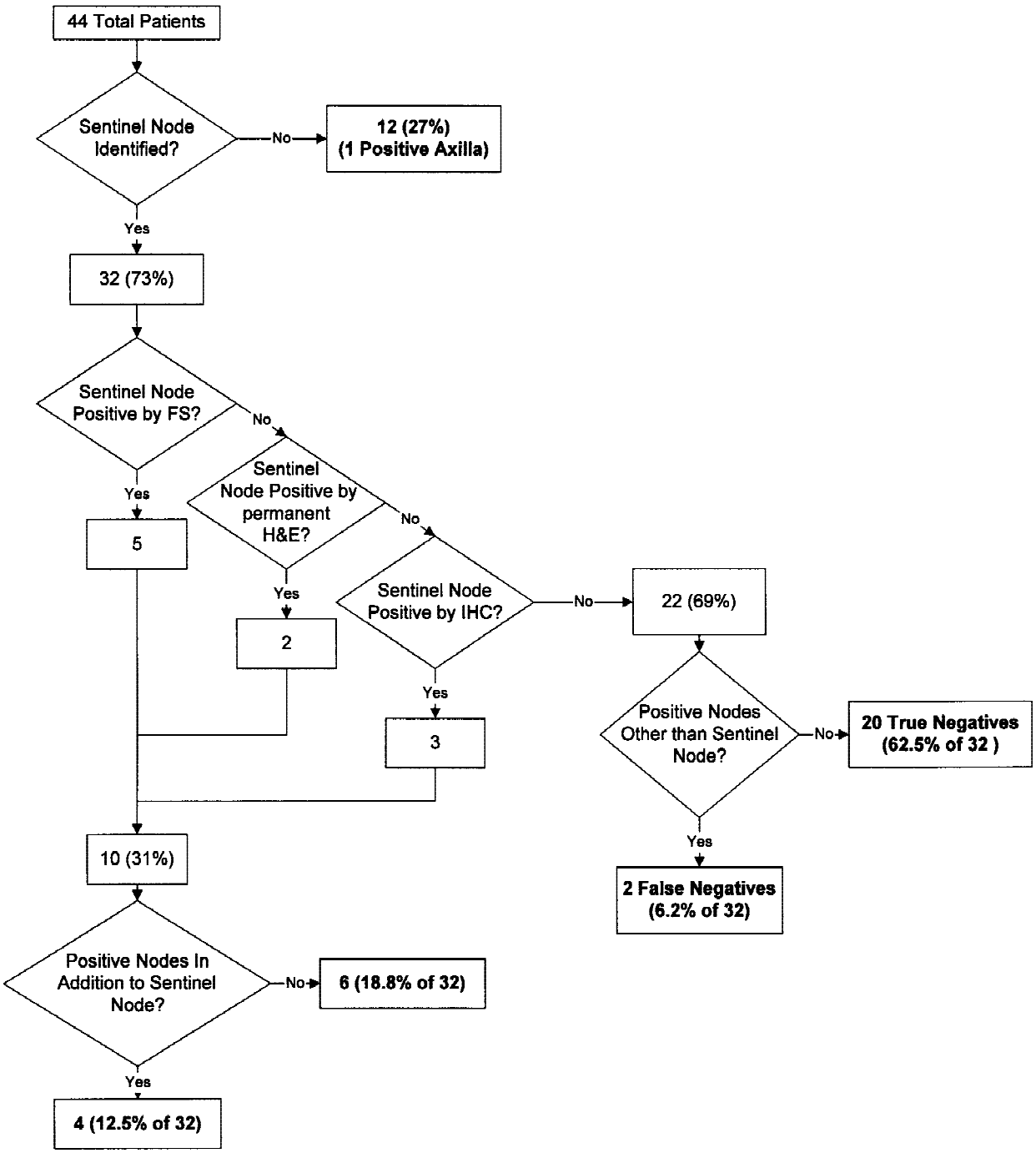

Fig. 1. Sentinel node detection rate and histology and nonsentinel node histology in 44 women treated for palpable invasive breast cancer. FS = frozen section; H&E = permanent hematoxalin–eosin stain; IHC = immunohistochemistry.

for each patient. Tumor in the first node may impede lymphatic flow to others in the chain. We began this series injecting immediately after skin preparation prior to draping, aiming to reach the lymphatics about 15 min after injection. We now inject before the skin preparation and apply gentle massage during washing to help move dye into the lymphatics. This also allows a little more time for dye to reach the sentinel node(s), particularly when the tumor is located further away than the upper-outer quadrant.

In addition, we have now begun sampling nodes subjacent to the actual blue node, whether or not they are stained. This practice seems to be in agreement with that used in other studies, which report the average number of "sentinel nodes" sampled between 1.8 and 2.6 [8, 11, 12, 16, 17]. In two of these studies, the number of sentinel

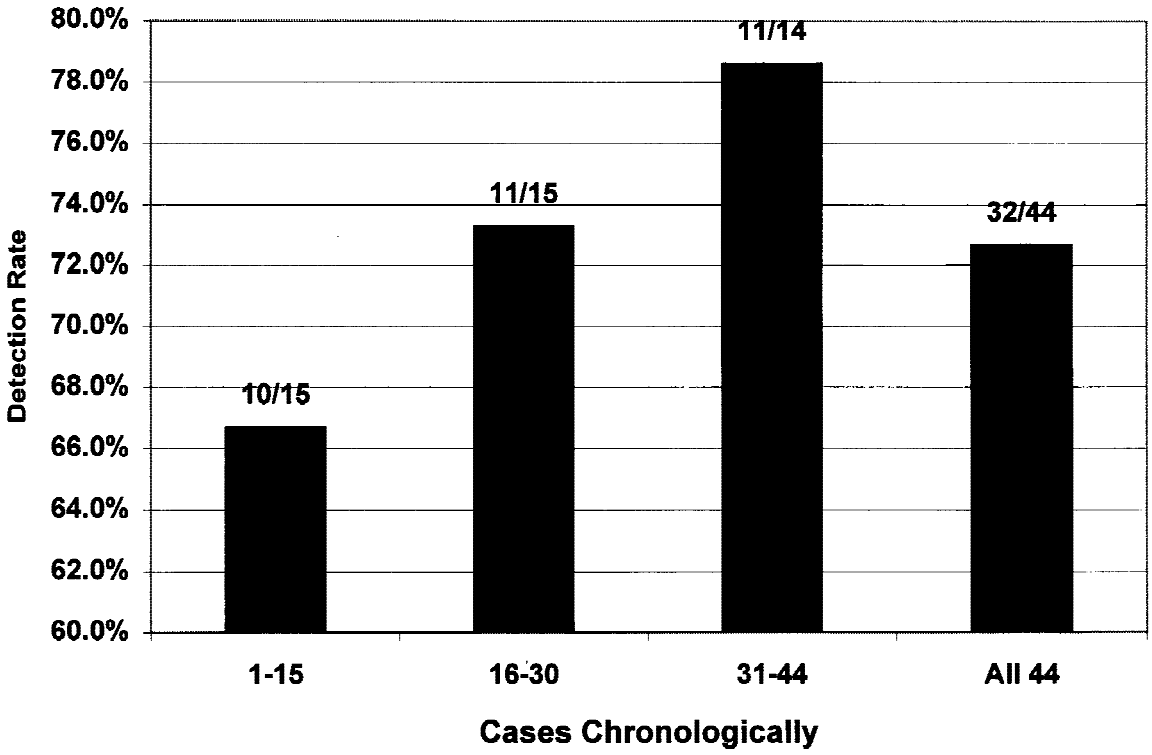

Fig. 2. Sentinel node detection rate for the first 15, second 15, last 14, and combined 44 patients using the isosulfan blue dye technique.

nodes ranged from 1 to 8, and the false negative rates were lower (3–5%) than the 6.2% we found in our series [11,17]. The question then arises: What is an appropriate level of sentinel node sampling? The simple definition that "the sentinel node is the first lymph node to receive lymphatic drainage from a tumor" [18] is obviously insufficient as a guideline for biopsy. Others have defined the sentinel node more specifically related to the mapping technique. Albertini et al. [8] indicate that a node is considered a sentinel node if it stains blue or has an in vivo radioactive count (via lymphoscintigraphy) 10 times greater than a neighboring nonsentinel lymph node, yet others describe sampling the blue and/or radioactively "hot" node(s) plus nodes subjacent to these [12,17]. Clearly, the probability of obtaining a false negative when sampling 6 or 8 nodes is less than what we would expect when sampling 1 or 2 nodes. At this point, however, we do not know if there is greater morbidity associated with this difference in sentinel node sampling. If and when the medical community at large adopts sentinel lymph node biopsy for breast cancer as a viable alternative to axillary dissection, the definition of appropriate sentinel node sampling will require further clarification.

Even if more "sentinel nodes" are sampled, it is inevitable that a few patients will have disease left in the axilla by misleading sampling or variability in the histologic interpretation of the frozen section. Thus, some will have axillary or more distant disease found at follow-up. A few patients (12% in our series) will have a change of status demonstrated by permanent H&E-stained sections and, more importantly, by IHC stains. In addition, the ability of the pathologist to study single nodes in considerable detail is a distinct advantage. Normally, all axillary nodes removed in a standard dissection are cut once, and one slide is made of each. In comparison, a sentinel node is sectioned many times.

It is also important that both the surgeons performing sentinel node mapping/biopsy and the pathologists performing the histologic evaluation follow standardized protocols. The pathology protocol should specify not only assays and methods but also the format for reporting and presenting results. A joint reading session may help in obtaining diagnostic consensus.

A significant number of patients who are candidates for sentinel node mapping/biopsy stand to benefit from the procedure. In this series of patients with T1 and T2 palpable invasive tumors, 45% would have been eligible to forego complete axillary dissection on the basis of the histologic status of their sentinel node(s). However, to enable the patient to make an informed decision regarding sentinel node biopsy as a potential alternative to axillary dissection, they should be provided the following information: (1) the likelihood of having their sentinel nodes found and if found, they will not contain cancer (45% in this series); (2) if the patient actually does have disease in their axilla, the likelihood of missing that disease when only the sentinel lymph nodes are assessed (100% − sensitivity = 16.7% in this series); and (3) the

likelihood of developing lymphedema or other complications should they require a complete axillary dissection (5.5%–80%) [19].

For some women, particularly those who have relatives or friends who have struggled with lymphedema, the decision could be relatively easy. However, we should encourage all patients to weigh the risks and potential benefits very carefully before making this decision.

CONCLUSIONS

This limited series indicates that sentinel node mapping and biopsy can be performed successfully in a community hospital setting with results comparable to those obtained at larger institutions. Sufficient training, certification, and quality control are necessary components of such a program. Improving the sensitivity of this test should remain a primary goal, however, if benign sentinel node histology is to be used as criteria to preclude axillary dissection.

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COMMENTARY

Axillary sentinel lymph node examination offers advantages of efficiency in detection of lymph nodal metastases and an opportunity to avoid more extensive axillary dissection in patients who have no detectable axillary metastases. Efficiency is gained because one or several sentinel nodes can be subserially sectioned to find tiny metastases with relatively little labor. Axillary dissection can be avoided with a $\leq$5% risk of misclassification because >95% of positive axillae are detected by sentinel node examination (negative predictive value exceeds 95% in a majority of reports).

A. Morgan and associates report start-up experience using blue dye. Their success rate of 73% in identification of sentinel nodes is characteristic for beginners and improved with experience. Use of a radiolabel may also increase success, as they have acknowledged. The somewhat high 6.2% false-negative rate they observed is attributable to inexperience and a consequence of their technique of sentinel node examination whereby they sectioned only the faces of the embedded blocks. They prepared three slides each containing several 4-μm sections, a total of 64 μm if each slide had 4 sections. Tissue blocks were 3- tor 4-mm thick. Thus, they examined 0.064/3 (0.021, or roughly 2%) of each 3-mm-thick block. The probability of finding a metastasis 1 mm in diameter by this technique is about 50%, and the probability of finding a 0.1-mm-diameter metastasis is about 6% percent [1]. The chance of finding metastases of these sizes would be similar in nodes from axillary dissections. If examination of sentinel nodes is conducted by subserial sectioning while other nodes are sectioned only once, then the probability of finding metastases in the sentinel node will be higher, and the probability of finding them in nonsentinel nodes and not in the sentinel nodes will be correspondingly lower.

Sentinel nodes should be subserially sectioned at equal, predetermined intervals in order to produce predictable levels of efficiency in metastasis detection. We do not yet know enough about cost-benefit ratios to decide what the interval should be, but nodal stage remains a most powerful prognostic factor for breast carcinoma. This argues that we should carry out a search strategy that will guarantee finding micrometastases at a low size

threshold. Opinions have been advanced to the effect that systematic search will fail to increase yield of metastases [2]. This point of view is attractive economically but is inconsistent with geometric prinicples and with recent direct observation. A study by a group in Milan has shown that serial sectioning of lymph nodes at 50-μm intervals discovered additional metastases in nearly equal increments for 10 consecutive levels after the initial face section [3]. The face section is likely to find only metastases that approach or exceed the thickness of slices that are embedded in paraffin. If the portion of the node containing a micrometastasis is not in the plane of section examined, costly immunohistochemical stains will be of no avail.

Sentinel node biopsy is a procedure of considerable power for detection of lymph nodal metastases, and Morgan et al. have demonstrated that it can be carried out successfully in the community. We should grasp this opportunity to the fullest by employing well-planned examination of the sentinel nodes that are obtained. Thereby we can learn more about the early phases of lymph node metastasis and their clinical meaning.

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